

enza through the use of antiviral agents with different mechanisms of action (e.g., baloxavir treatment combined with postexposure prophylaxis with oseltamivir in long-term care facility residents). Data are lacking on the efficacy, effectiveness, appropriate dose administration, or duration of baloxavir use for the treatment or postexposure prophylaxis of novel influenza A viruses of pandemic potential, including highly pathogenic avian influenza A(H5N1) virus, which limits the use of baloxavir in real-world public health strategies. During the early phase of an influenza pandemic, when pandemic influenza vaccines are not yet available, early treatment with baloxavir, with its ability to decrease viral shedding, might have greater benefit in reducing transmission than when it is used for seasonal influenza, because most exposed persons will lack specific immunity to the pandemic influenza virus and household transmission is expected to be high.

The findings and conclusions in this editorial are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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Clonal Hematopoiesis as a Driver of Solid Tumors

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Clonal hematopoiesis is the expansion of a genetically related population of hematopoietic stem and progenitor cells that disproportionately contribute to blood-cell production.¹ Clonal hematopoiesis of indeterminate potential (CHIP) is defined by mutations in genetic drivers of myeloid cancers, a variant allele fraction of 2% or more, and the absence of cytopenias. CHIP is powerfully associated with the development of myeloid cancers such as myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). The risk of progression from CHIP to MDS or AML varies, and features such as specific mutations, clone size, number of mutations, red-cell variables, and patient age have clear prognostic importance.²

CHIP mutations are also associated with aberrant blood-cell function, resulting in an increased incidence and more aggressive phenotypes of select age-related nonmalignant diseases, including atherosclerotic heart disease, gouty arthritis, giant-cell arteritis, and chronic liver disease.¹ In animal models, the presence of specifically *Tet2*-mutant hematopoietic cells leads to enhanced intraarterial inflammation, accelerated formation of atherosclerotic plaque, and other inflammatory phenotypes.¹ In cohort studies involving humans as well as in murine models, *TET2* or *Tet2* mutations are associated with elevated levels of interleukin-1 β . In CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcome Study), a

phase 3 clinical trial of an interleukin-1 β inhibitor for the treatment of cardiovascular disease, exploratory analysis showed the most dramatic reductions in cardiovascular disease risk among canakinumab-treated participants with *TET2*-mutant CHIP.³

Inflammation is also recognized as a key component of tumor initiation and cancer progression, with several examples of cancers arising in sites of chronic epithelial inflammation or infection. Retrospective analysis of CANTOS showed that participants who had received canakinumab had a 67% lower incidence of lung cancer after 3.7 years of follow-up than those who had received placebo.⁴ Observations of tumor progression and related survival disadvantage in patients with solid tumors who have clonal hematopoiesis raise the question of whether clonal hematopoiesis-informed antiinflammatory targeting of cancer may have particular clinical benefit.

In this issue of the *Journal*, Pich et al. leverage two cancer cohorts to analyze the effect of both circulating CHIP and tumor-infiltrating clonal hematopoiesis (TI-CH) on outcomes in persons with solid tumors.⁵ The authors found that TI-CH was common among persons with circulating CHIP. In a cohort of 421 patients with early-stage

lung cancer from the TRACERx (Tracking Non-Small-Cell Lung Cancer Evolution through Therapy) cohort, TI-CH was detected in 42% of patients with CHIP; in the overall cohort, patients with TI-CH had nearly twice the risk of death or disease recurrence as those without TI-CH. Affirming these findings in an independent cohort, the authors found that TI-CH was present in 26% of patients with CHIP identified in a 49,351-person MSK-IMPACT (Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets) pan-cancer cohort and was again associated with an increased risk of death from any cause.

Analysis of the MSK-IMPACT pan-cancer cohort showed that TI-CH prevalence varied substantially across cancer types. For instance, TI-CH was enriched in non-small-cell lung cancer, head and neck cancer, pancreatic cancer, and mesothelioma as compared with other types of solid tumors. In addition, although TI-CH was prevalent in metastatic samples, TI-CH was not detected in all metastatic lesions, even in the same patient. Although the authors suggest that distinct organotropism may explain differential detection of TI-CH among metastatic lesions, the organ specificity of TI-CH detection remains largely unexplored.

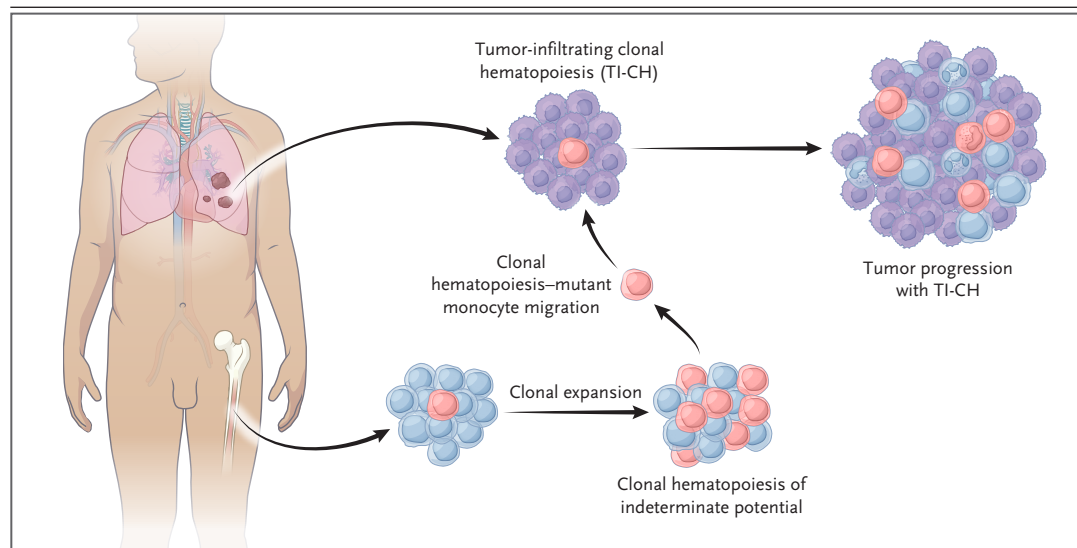


Figure 1. Tumor-Infiltrating Clonal Hematopoiesis and Progression of Solid Tumors.

Adults with solid tumors may have concomitant circulating clonal hematopoiesis, which on clonal expansion is referred to as clonal hematopoiesis of indeterminate potential (or CHIP). Pich et al.⁵ report that tumor-infiltrating clonal hematopoiesis (TI-CH) occurs as the result of homing of clonal hematopoiesis-mutant monocytes into solid tumors. This phenomenon, which has some specificity for *TET2*-mutant clonal hematopoiesis, is associated with tumor progression.

The finding that *TET2*-mutant CHIP was the strongest genetic predictor of TI-CH is well aligned with the findings of previous studies linking *TET2*-mutant CHIP to systemic and local inflammation. Functional studies support the association between *TET2* and TI-CH by showing preferential migration of *TET2*-mutant monocytes toward lung cancer cells, differentiation of *TET2*-mutant myeloid cells into CD11+ macrophages in the tumor microenvironment, and enhanced organoid growth in cocultures with *TET2*-mutant myeloid cells (Fig. 1). Future work may explore how the aberrant proinflammatory cytokine activity that drives nonmalignant phenotypes in circulating *TET2*-mutant CHIP is connected to the protumorigenic capacity of *TET2*-mutant TI-CH. Such a link may provide at least a partial explanation for the 36% increased incidence of lung cancer among persons with CHIP.⁶

Antiinflammatory therapies may have antitumor efficacy, but this has not been shown in prospective studies of interleukin-1 β inhibition in lung cancer. Future trial efforts could build on the genotype-specific effects of TI-CH to restrict enrollment to TI-CH genotypes most likely to derive benefit from interleukin-1 β inhibition. Whether antiinflammatory therapies would prevent cancer initiation in solid-tumor precursors or prevent metastasis of localized cancers are also intriguing matters for future investigation.

In all, these data robustly demonstrate the prognostic significance of TI-CH, building on preliminary findings in smaller cohorts and underscoring the complex interplay between age-related expansion of clonal hematopoiesis and inflammatory cells within the solid-tumor microenvironment. As with other CHIP phenotypes, the ob-

served CHIP-associated solid-tumor progression is a genotype-specific phenomenon, but the biologic factors underlying genotype specificity remain to be elucidated. This novel characterization of the prognostic significance of TI-CH positions TI-CH, rather than circulating CHIP, as a potential target for interventions that regulate tumor progression and metastasis in solid cancers.

Many questions remain unanswered. Why is TI-CH detected in some persons with CHIP and not in others? What is the explanation for varied TI-CH detection in metastatic lesions? And perhaps most importantly, in what ways can tumor homing of CHIP cells be therapeutically manipulated to prevent cancer-related deaths?

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